American Journal of Hematology 58:339–342 (1998)

LETTERS AND CORRESPONDENCE

Letters and correspondence submitted for possible publication must be identified as such. Text length must not exceed 500 words and five bibliographic references. A single concise figure or table may be included if it is essential to support the communication. Letters not typed double-spaced will not be considered for publication. Letters not meeting these specifications will not be returned to authors. Letters to the Editor *are utilized to communicate a single novel observation or finding.* Correspondence *is to be used to supplement or constructively comment on the contents of a publication in the journal and cannot exceed the restrictions for* Letters to the Editor. *The Editor reserves the right to shorten text, delete objectional comments, and make other changes to comply with the style of the journal. Permission for publication must be appended as a postscript. Submissions must be sent to Marcel E. Conrad, M.D., Associate Editor,* American Journal of Hematology, *USA Cancer Center, Mobile, Alabama 36688 to permit rapid consideration for publication.*

Infiltration of the Central Nervous System as a Presentation Form of Early Stage Chronic Lymphocyte Leukemia

To the Editor: Symptomatic infiltration of the central nervous system by chronic lymphocytic leukemia (CLL) is extremely rare [1] and is accompanied by cerebro-spinal fluid (CSF) lymphocytosis. In autopsy series [2], however, infiltration of the brain or spinal cord is common in CLL, particularly in later stages, but patients are asymptomatic. We present a case of CLL (Rai stage 0), which began with neurological manifestations, secondary to leukemic meningeal infiltration.

A 65-year-old man with a history of chronic liver disease due to hepatitis C virus was admitted with progressive headache, weight loss, and night sweats, recently accompanied by confusion, diplopia, and dysphagia. Physical examination revealed no peripheral lymphadenopathies or visceromegalies. The WBC count was 25×10^9/l (59% lymphocytes, 33% neutrophils). Peripheral smear lymphocytes were predominantly mature with 15% prolymphocyte forms. Hemoglobin was 13.4 g/dl and platelets 205×10^9/l. Chest and abdominal CT scans were normal, as were cranial MRI and CT scans. A lumbar puncture gave a WBC count of 586/mm^3 (85% lymphocytes morphologically similar to those in the peripheral blood). Extensive microbiological studies were negative. A bone marrow smear and biopsy showed a diffuse infiltration of mature lymphocytes and 20% prolymphocyte forms. Phenotyping of the lymphoid population of the CSF and peripheral blood showed a monoclonal lambda light chain expression, a positive result for CD_{19}, FMC7, CD_{23}, and coexpression of CD_{19} and CD_5, in 87% of the cells. B cell CLL Rai stage 0, with meningeal infiltration, was diagnosed. Polychemotherapy was initiated according to the COP scheme, with intrathecal methotrexate being added on days 1 and 10 of each cycle. After the first cycle the patient showed a clear improvement in neurological signs and the CSF WBC count fell to 60/mm^3. He died after the second cycle of chemotherapy due to bilateral pneumonia. No autopsy was performed.

The finding of neurological symptoms as the initial manifestation of the disease is exceptional, and only a few cases have been reported (Table I). In our case, although the diagnosis of B cell CLL was suspected from the morphological and cytochemical findings in the peripheral blood and bone marrow, the monoclonal character of the lymphocyte proliferation needed to be shown to provide confirmation. This monoclonality was demonstrated by the presence of a single lambda light chain on the cell surface of B lymphocytes by flow cytometry [3]. The positive result of CD_{23} in the absence of lymphadenopathies or splenomegaly ruled out the possibility of a mantle lymphoma, which should always be considered in the differential diagnosis [4]. The positive result for FMC7 was interpreted as the expression of a possible evolutionary stage towards a prolymphocytic leukemia. Finally, the importance of immunophenotyping CSF lymphocytes to reach a diagnosis of CNS infiltration by CLL should be noted. When faced with a neurological picture with peripheral lymphocytosis, even in the absence of peripheral lymphadenopathies and visceromegalies, CLL should be included in the differential diagnosis, as, although its incidence is low, methods are available to confirm the tumoral origin of the proliferation, as well as to provide specific therapy.

I. PÉREZ FERNÁNDEZ
Hematology Service, "Virgen de la Victoria"
University Hospital, Málaga, Spain

F. SALGADO ORDÓÑEZ
Internal Medicine Service, "Virgen de la Victoria"
University Hospital, Málaga, Spain

TABLE I. Symptomatic Infiltration of CNS: A Presentation Form of CLL*

Reference	Sex/age	Stage[a]	CNS localization	Neurological findings
Korsager et al. [5]	F/64	II	CSF	Dementia
Cash et al. [6]	M/59	0	CSF	Blindness
	M/47	0	CSF	Headache/gait disturbance
Fain et al. [7]	F/57	II	Pituitary CSF	Bitemporal hemianopsia; panhypopituitarism
Cramer et al. [2]	F/87	0	Subarachnoid	Agitated
Current report	M/65	0	CSF	Headache; confusion

*CNS, central nervous system; CLL, chronic lymphocytic leukemia; CSF, cerebro-spinal fluid.
[a]At diagnosis of CNS involvement.

A. Rueda Dominguez
I. Sevilla García
Medical Oncology Service, ''Virgen de la Victoria'' University Hospital, Málaga, Spain
A. Siles Rodriguez
Hematology Service, ''Carlos Haya'' Regional Hospital, Málaga, Spain

References

1. Montserrat E, Rozman C: Chronic lymphocytic leukemia: Present status. Ann Oncol 6:219–235, 1995.
2. Cramer S, Glaspy JA, Efird J, Louis D: Chronic lymphocytic leukemia and the central nervous system. Neurology 46:19–25, 1996.
3. Dighiero G, Travade P, Chevret S, Feneaux P, Chastang C, Binet JL: B cell chronic lymphocytic leukemia: Present status and future directions. Blood 78:1901–1914, 1991.
4. Harris NL, Jaffe ES, Stein H, Banks PM, Chang JKC, Cleary ML: A revised European-American classification of lymphoid neoplasms: A proposal from the International Study Group. Blood 84:1361–1392, 1994.
5. Korsager S, Lawsen B, Mortensen TM: Dementia and central nervous system involvement in chronic lymphocytic leukemia. Scand J Haematol 29:283–286, 1982.
6. Cash J, Fehir KM, Pollack MS: Meningeal involvement in early stage chronic lymphocytic leukemia. Cancer 59:798–800, 1987.
7. Fain JS, Naeim F, Becker DP, Van Herle A, Yan-Go F, Petrus L: Chronic lymphocytic leukemia presenting as a pituitary mass lesion. Can J Neurol Sci 19: 239–242, 1992.

Dose-Dependent Pulmonary Syndrome in Patients With Thalassemia Major Receiving Intravenous Deferoxamine

To the Editor: Desferrioxamine (DFO) is the main iron chelator for the treatment of iron overload in patients with β-thalassemia major requiring transfusion therapy [1]. Intensive chelation therapy with intravenous (IV) DFO has been shown to improve cardiac function in patients with pre-existing iron-induced damage to the heart [2]. Moreover, high IV doses of DFO have been used to enhance iron chelation in patients with excessive iron burdens and significantly increased the urinary excretion of iron [2,3]. Between 1991 and 1997, we have administered 33 courses of high-dose IV DFO to 17 patients with β-thalassemia major, whose serum ferritin levels ranged from 1,986 to 18,700 ng/mL (mean: 5,400 ng/mL, SD: ± 4,174 ng/mL). All of them were previously receiving daily 10-hr subcutaneous (SC) administration of DFO at doses of 25 to 50 mg/kg/d. We observed the development of a DFO dose-dependent pulmonary syndrome in 2 of these patients. Apart from occasional complaints of cramping due to hypocalcemia, no other side effect was observed with the treatment.

In the first 14 courses (1991 to 1995), a 10-day continuous IV-DFO infusion was administered in which the doses were increased from 2 to 10 mg/kg/hr, and this maximum dose was maintained for 3–5 days (Protocol A, Table I). None of these patients presented respiratory abnormalities during the IV-DFO treatment. Encouraged by the impressive degrees of urinary iron excretion, we extended the duration of the maximum dose administration to 8–10 days (Protocol B, Table I). Between 1995 and 1997, 19 IV-DFO courses were administered to 10 patients according to Protocol B. All patients shared the same features from the previous protocol, 5 of whom received both protocols. The two cases of respiratory dysfunction were observed with Protocol B. The first patient was an 11-year-old girl, who had never received IV DFO before and presented serum ferritin of 2,600 ng/mL. She developed low fever and malaise on the 6th treatment day, followed on the 8th day by tachypnea and tachycardia, and the arterial blood gases measurement disclosed hypoxemia and hypocapnia (arterial pO_2: 26 mm Hg, and pCO_2: 28 mm Hg, pH: 7.3). The chest X ray showed a bilateral extensive intersticial infiltrate. Cultures, contra-immune-electrophoresis to fungi, ELISA to tuberculosis, and mycoplasma and viral titers failed to identify an infectious agent. The respiratory impairment was life-threatening and required mechanical ventilation support for 2 weeks. Two weeks after recovery, the pulmonary function was evaluated and showed a restrictive pattern with a decrease in predicted response for total lung capacity, forced vital capacity, and forced expiratory volume. After 8 months the pulmonary function had returned to normal.

The second case was observed in a 15-year-old girl, with serum ferritin of 3,900 ng/mL. She received 2 courses of IV DFO according to protocol B within 8 months. She developed the pulmonary syndrome on the 10th day of the 2nd treatment, presenting malaise, low fever, and nausea, followed after 24 hr by mild dyspnea with tachypnea. However, the hypoxemia was less severe than in the preceding case (arterial pO_2: 69 mm Hg, pCO_2: 31 mm Hg, pH: 7.46) requiring only the use of O_2 mask for 5 days. The chest X ray disclosed a similar interstitial infiltrate. There was no laboratory evidence of infection and no abnormalities were detected by pulmonary function studies. In both cases, after discharge, the SC DFO administration was reintroduced without complication.

Analyzing the variables, total DFO dose, rate of infusion, length of treatment, previous use of IV DFO, age, and serum ferritin, we detected a significantly higher risk of presenting the pulmonary syndrome in patients who had a DFO rate of infusion higher than 8 mg/kg/hr for more than 4 days ($P = 0.04$).

The syndrome described here is similar to the one reported by Freedman et al. [4] in 4 of 8 patients with β-thalassemia major receiving IV DFO in doses ranging from 10 to 22 mg/kg/hr for 5 to 9 days. These authors performed lung biopsies in 2 patients, which showed a diffuse alveolar damage, interstitial fibrosis, and an inflammatory infiltrate (containing IgE^+ cells) in one case. By comparing the DFO dose and the rate of infusion with the frequency of pulmonary abnormalities observed in protocols A and B and the data reported by Freedman et al. [4], the relevance of the dose and the length of the DFO infusion become evident. This observation is in agreement with Tenebein et al. [5], who treated 43 cases of iron poisoning treated with IV DFO in doses of 15 mg/kg/hr and found that among the 14 patients who were treated for longer than 24 hr, 8 presented pulmonary dysfunction. Studies in human and animals suggest that the toxic pulmonary effects of DFO are probably related to free-radical generation [6].

Eduardo Magalhães Rego
Edmir Botturão Neto
Belinda Pinto Simões
Marco Antonio Zago
Department of Internal Medicine, Medical School of Ribeirão Preto, University of São Paulo, Ribeirão, Preto, SP Brazil

TABLE I. High-Dose IV DFO Protocols Administered to 17 β-Thalassemia Major Patients*

DFO treatment	Total DFO dose (g)	Daily dose (mg/kg/d)	Maximum dose (mg/kg/hr)	Maximum dose duration (days)	Pulmonary syndrome frequency
Protocol A	60.7	157.6 ± 34.4	8.7 ± 1.6	3.86 ± 0.9	0/14
Protocol B	71.9	166.2 ± 39.6	7.9 ± 1.8	7.75 ± 2	2/19

*Values = mean ± SD.

References

1. Giardina PJ, Grady RW: Chelation therapy in β-thalassemia: The benefits and limitations of desferrioxamine. Semin Hematol 32:304, 1995.
2. Cohen AR, Martin M, Schwartz E: Current treatment of Cooley's anemia. Intravenous chelation therapy. Ann NY Acad Sci 612:286, 1990.
3. Cohen A, Mizanin J, Schwartz E: High-dose intraveneous chelation therapy with deferoxamine. In Buckner CD, Gale RP, Lucarelli G (eds): Advances and Controversies in Thalassemia Therapy. New York: Alan R. Liss Inc., 1989.
4. Freedman MH, Grisaru D, Olivieri N, MacLusky I, Thorner PS: Pulmonary syndrome in patients with thalassemia major receiving intravenous deferoxamine infusions. Am J Dis Child 144:565, 1990.
5. Tenenbein M, Kowalski S, Sienko A, Bowden DH, Adamson IY: Pulmonary toxic effects of continuous desferrioxamine administration in acute iron poisoning. Lancet 339:699, 1992.
6. Adamson IY, Sienko A, Tenebein M: Pulmonary toxicity of deferoxamine in iron-poisoned mice. Toxicol Appl Pharmacol 120:13, 1993.

Congenital Spherocytic Hemolytic Anemia in a Family Presenting With Transient Red Cell Aplasia From Parvovirus B19 Infection

To the Editor: Transient aplastic crisis (TAC) is associated with parvovirus B19 infection in individuals with an underlying hemolytic process and has been reported in patients with hemoglobinopathies, hereditary spherocytosis, red cell enzymopathies, and autoimmune hemolytic anemia [1]. Small outbreaks of TAC have been reported in communities with a significant percentage of hemoglobinopathies [2]. We report the development of TAC in a 5-year-old child and the subsequent development of a TAC, 2 weeks later, in the mother, which led to the diagnosis of congenital spherocytic anemia. Parvovirus B19 was isolated from the marrow of both cases.

A 5-year-old male child was admitted with a diagnosis of severe anemia (Hb 52 g/l, platelets $150 \times 10^9/1$, WBC $7.4 \times 10^9/1$). The reticulocyte count was low ($37 \times 10^9/1$) but some normoblasts and atypical lymphoid cells were seen in the peripheral film and a malignancy in the bone marrow was suspected. The marrow was cellular with marked erythroid hyperplasia, essentially at the early to intermediate normoblast stage. No evidence of dyserythropoiesis or inclusions was seen. The possibility of a recovering TAC was raised and the child was observed with later recovery of the reticulocyte count and hemoglobin. Spherocytosis also became evident in the peripheral blood. Two weeks later the mother was admitted by another physician with symptoms of jaundice, fever, and nausea of 1-week duration. Her Hb, which had been 110 g/l, fell to 66 g/l, her WBC was $3.9 \times 10^9/1$, platelet count $64 \times 10^9/1$, and reticulocyte count $44 \times 10^9/1$. Marrow examination showed marked erythroid hyperplasia at an early to intermediate stage. After observation, the Hb, reticulocyte count, and platelets returned to normal. Spherocytosis, which had been noted in the peripheral blood at admission, became more evident. Parvovirus B19 was detected in material stained from paraffin-embedded marrow particles by PCR using primers B19-1 and B19-2 [3]. A positive result was indicated by the presence of a 104-bp band (Fig. 1).

Infection with parvovirus B19 is common with some studies showing more than 90% of elderly people having detectable antibody and 50% of children by the age of 15 [1]. Infection is usually asymptomatic but may give rise to other disorders such as erythema infectiosum, polyarthropathy, and hydrops fetalis in pregnancy [1]. As the blood group P antigen acts as a receptor for the virus [4], the virus has a predilection for the red cell series and infection is usually associated with temporary red cell aplasia. In normal individuals, this is unnoticed and only becomes a crisis in patients with an underlying hemolytic disorder or in immunocompromised individuals where the virus cannot be eliminated. In the two cases presented, it was the aplastic crisis precipitated by the parvovirus B19 infection that exposed the underlying disorder, namely congenital spherocytic hemolytic anemia. The diagnosis (TAC) must be considered in children presenting with severe anemia, reticulocytopenia, and sometimes thrombocytopenia particularly as by the time the peripheral blood is examined there may be normoblasts in the peripheral blood along with the low reticulocyte count, suggesting a malignancy.

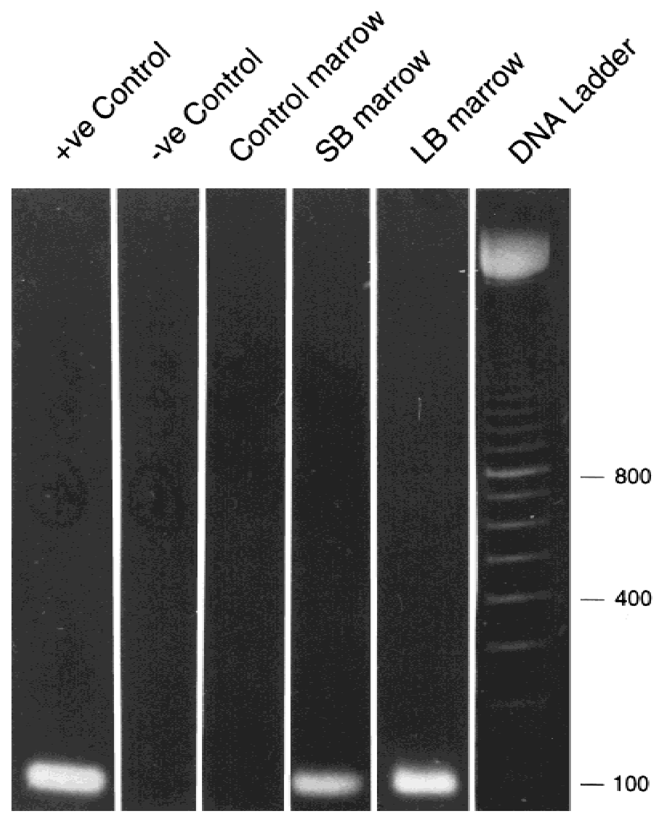

Fig. 1. Results of PCR amplification of material from paraffin-embedded marrows with primers B19-1 and B19-2 for parvovirus. A positive result is indicated by the presence of a 104 bp band.

L.F. Skinnider
Department of Pathology, University of Saskatchewan, Saskatoon, Canada

B.J. McSheffrey
Department of Pediatrics, University of Saskatchewan, Saskatoon, Canada

D. Sheridan
Department of Medicine, University of Saskatchewan, Saskatoon, Canada

H. Deneer
Department of Microbiology, University of Saskatchewan, Saskatoon, Canada

References

1. Brown KE, Young NS, Johnson ML: Molecular, cellular and clinical aspects of parvovirus B19 infection. Crit Rev Oncol Hematol 16:1–31, 1994.
2. Mallough AA, Qudah A: An epidemic of aplastic crisis caused by human parvovirus B19. Pediatr Infect Dis J 14:31–34, 1995.
3. Salimans MM, Holsappel S, Van de Rijke FM, Jiva NM, Raap AK, Wieland HT: Rapid detection of human parvovirus B19 DNA by dot-hybridization and the polymerase chain reaction. J Virol Methods 23:19–28, 1989.

4. Brown KE, Anderson SM, Young NS: Erythrocyte P antigen: Cellular receptor for B19 parvovirus. Science 262:114–117, 1993.

Progression of a Myelodysplastic Syndrome With Trisomy 8 to Acute Lymphoblastic Leukemia

To the Editor: The myelodysplastic syndromes (MDS) are characterized by the expansion of an abnormal clone of hematopoietic stem cells and maturation abnormalities [1]. In general, the majority of leukemic transformation in MDS develop acute myeloid leukemia, but the progression to acute lymphoblastic leukemia (ALL) rarely occurs [2]. We present a patient who developed ALL during the course of MDS with trisomy 8 and myelofibrosis.

A 43-year-old Japanese female was admitted with low-grade fever and diarrhea in March 1993. She had been followed with Behçet disease since 1984. The peripheral blood examination showed pancytopenia. A bone marrow aspiration demonstrated trilineage dysplasia with 12% blasts. A bone marrow biopsy specimen showed focal myelofibrosis. Cytogenetic studies on the bone marrow revealed trisomy 8 in all 20 metaphases. She was diagnosed with refractory anemia with excess of blasts (RAEB) with myelofibrosis. She was followed as an outpatient without specific treatment. She had splenomegaly without changes of laboratory data in October 1995. One year later she was admitted again because of increasing blasts in the peripheral blood. The peripheral blood showed: white blood cells 25.5×10^9/l with 50% blasts, hemoglobin 11.6 g/dl, and platelets 31.0×10^9/l. A bone marrow aspiration was not successful because of ‘‘dry taps.’’ A bone marrow specimen obtained by biopsy demonstrated decreased normal hematopoietic elements, increased blasts, and proliferation of reticulin and collagen fibers. Blasts in the peripheral blood were negative for peroxidase, but were slightly positive for periodic acid Schiff. The immunophenotyping by flow cytometry revealed that the blasts had cell surface markers consistent with B-ALL: CD1(-), CD2(-), CD3(-), CD4(-), CD5(-), CD7(-), CD8(-), CD10(+), CD13(-), CD14(-), CD19(+), CD20(+), CD33(-), and HLA-DR(+). Cytogenetic analysis was as follows: fourteen of twenty metaphases showed trisomy 8 and the remaining six showed a deletion in the short arm of a chromosome 9 and an addition of the short arm of a chromosome 10. Gene rearrangement study for the T cell receptor beta chain was rearranged, while the IgH gene was in germline configuration. She received combination chemotherapy of l-asparaginase, vincristine, and prednisolone for induction therapy in November 1996. The effect of chemotherapy resulted in a decrease in blasts, and improvement of myelofibrosis and splenomegaly were obtained. She was treated with additional chemotherapy and is undergoing a bone marrow transplantation.

Trisomy 8 is one of the more common cytogenetic abnormalities in primary MDS, while this abnormality is a very rare finding in de novo ALL [3]. Nevertheless, it has been reported that trisomy 8 is observed in lymphoid blasts in a case developing from MDS to pre-B ALL by using fluorescence in situ hybridization analysis [4]. Therefore, it should be considered that this patient's myelodysplastic process evolved into ALL. This case, together with others in the literature [2,4,5], is consistent with the hypothesis that leukemic transformation from MDS involves a pluripotent stem cell that has the potential for lymphoid commitment.

Aki Mishima
Mami Aoba
Satoshi Yamaji
Jun Taguchi
Heiwa Kanamori
Shigeki Motomura
Hiroshi Mohri
Takao Okubo
First Department of Internal Medicine, Yokohama City University School of Medicine, Yokohama, Japan

References

1. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG, Gralnick HR, Sultan C: Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 51:189–199, 1982.
2. Meckenstock G, Fontatsch Ch, Heyll A, Schneider EM, Koglor G, Sohngen D, Aul C, Schneider W: T-cell receptor τ/δ expressing acute leukemia emerging from sideroblastic anemia: Morphological, immunological, and cytogenetic features. Leuk Res 16:379–384, 1992.
3. Garipidou V, Yamada T, Prentice HG, Secker-Walker LM: Trisomy 8 in acute lymphoblastic leukemia: A case report and update of the literature. Leukemia 4:717–719, 1990.
4. Abruzzese E, Buss D, Rainer R, Pettenati MJ, Rao PN: Progression of a myelodysplastic syndrome to pre-B acute lymphoblastic leukemia: a case report and cell lineage study. Ann Hematol 73:35–38, 1996.
5. Kouides PA and Bennett JM: Transformation of chronic myelomonocytic leukemia to acute lymphoblastic leukemia: Case report and review of the literature of lymphoblastic transformation of myelodysplastic syndrome. Am J Hematol 49:157–162, 1995.